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Serum Phosphate and Cognitive Function in Older Men

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Abstract

Objective—Determine whether serum phosphate is associated with concurrent cognitive impairment and subsequent cognitive decline in older men independent of demographic covariates and atherosclerotic risk factors.

Methods—In a prospective study of 5,529 men enrolled in the Osteoporotic Fractures in Men (MrOS) study, we measured baseline serum phosphate, baseline cognitive function, and change in cognitive function between baseline and follow-up exams an average of 4.6 years later using the Modified Mini-Mental State (3MS) examination and Trails B.

Results—There was no association between serum phosphate and odds of cognitive impairment as assessed by baseline 3MS score or risk of cognitive decline as assessed by longitudinal change in 3MS score. Higher baseline serum phosphate was associated with higher odds of poor executive function as assessed by Trails B with fully adjusted odds ratios (OR) 1.12 (95% confidence interval [CI]: 0.83–1.52), 1.31 (0.97–1.77), and 1.45 (1.08–1.94) for men in the 2nd, 3rd, and 4th versus the bottom quartile (referent group) of serum phosphate (p-trend 0.007). However, higher phosphate level was not associated with risk of decline in executive function as assessed by longitudinal change in Trails B score with fully adjusted OR 0.94 (95% CI 0.69–1.28), 0.96 (0.70–1.32), 1.21 (0.89–1.66) for men in the 2nd, 3rd, and 4th versus the bottom quartile (referent group) of serum phosphate (p-trend 0.22).

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Conclusions—Higher serum phosphate in older men was associated with a higher likelihood of poor executive function, but not with impaired global cognitive function or decline in executive or global cognition.

Keywords

phosphate; cognitive function; elderly; men

INTRODUCTION

Renal function declines with age (Coresh et al. 2007); at least 20% of adults in the US aged 65 years have moderately to severely decreased kidney function. Kidney disease has been associated with cognitive impairment and dementia independently of traditional risk factors for atherosclerosis and risk of stroke (Kurella et al. 2004a; Kurella et al. 2005; Yaffe et al. 2010). Abnormalities of the bone metabolism parameters might contribute to the association. For example, low level of vitamin D (Annweiler et al. 2016) and high parathyroid hormone (Lourida et al. 2015) have been associated with poor cognitive function.

Although there is evidence from observational studies that high phosphorus levels are associated with greater risk of cardiovascular events in individuals without chronic kidney disease (CKD) (Foley 2007; Foley et al. 2008; Palmer et al. 2011), there is scarce data about the relationship between serum phosphate and cognitive function in individuals with and without kidney disease. Some (Kang et al. 2015; Kurella et al. 2004b), but not all (Shavit et al. 2014), previous investigations conducted in selected populations of patients with CKD or end stage renal disease (ESRD) have reported independent associations of higher phosphorus levels with cognitive function or decline. Our aims were to determine, in a cohort of community dwelling older men not selected on the basis of kidney disease, whether serum phosphate is associated with 1) concurrent cognitive impairment and 2) subsequent cognitive decline independent of demographic covariates and atherosclerotic risk factors.

METHODS

Participants

The Osteoporotic Fractures in Men (MrOS) Study is a multicenter prospective study of osteoporosis and other outcomes of aging in older men. The design, measures, and recruitment methods have been described previously (Blank et al. 2005; Orwoll et al. 2005). Five thousand nine hundred ninety-four men 65 years or older were recruited from March 2000 to April 2002 from six geographic regions of the United States. Approval was obtained from the institutional review boards of the participating institutions, and written informed consent was obtained from all study participants. Men were excluded from the study if they could not walk without assistance, had bilateral hip replacements, or had a severe medical condition that would preclude participation in follow-up. Among the men participating in the study, 461 did not have a serum phosphate measure at baseline and 4 did not have a baseline measure of cognitive function leaving an initial study sample of 5,529 (98.8% of initial cohort) for analyses examining phosphate level and cognitive function at baseline

(Figure 1). Of these, 5,528 and 5,403 had completed the Modified Mini-Mental State examination (3MS) and Trail Making Test B (Trails B) at baseline, respectively. An average (SD) of 4.6 (0.4) years later, cognitive function testing was repeated at a follow-up exam (Visit 2). Only those who were not cognitively impaired at baseline and who had repeated measures were included in the longitudinal analysis. As detailed in Figure 1, a total of 3,717 men were included in analyses examining baseline phosphate level and odds of decline in 3MS score and 3,713 men were included in analyses examining baseline phosphate level and odds of decline in Trails B test score.

Phosphate Assay

Fasting morning blood was collected, serum was prepared immediately after phlebotomy, and then was stored at -70°C . All samples remained frozen until assay. Phosphate was measured using a standard clinical automated analyzer. The lower limit of detection for serum phosphate was 0.3 mg/dL, and interassay coefficient of variation (CVs) was 2.4%. Normal levels vary by laboratory; they commonly are 2.5–4.9 mg/dL.

Cognitive Testing

Cognitive function was assessed by a trained technician with the 3MS examination and Trails B test at baseline and at the follow-up exam. The 3MS is a test of global cognitive function, with scores ranging from 0–100, with higher scores representing better cognitive function (Teng and Chui 1987). The Trails B test is a measure of executive function. It assesses attention, concentration, psychomotor speed, cognitive shifting and complex sequencing function by measuring the time required to connect a series of sequentially numbered and lettered circles. Shorter completion times indicate better performance, with test scores affected by age, education and general intelligence (Reitan 1958). For cross-sectional analyses, prevalent cognitive impairment was defined as having a baseline 3MS <88 (Shumaker et al. 2003) or a Trails B time greater than 1.5 standard deviations above the mean (>223.2 seconds). For prospective analyses, cognitive decline was defined as having the change in 3MS score from visit 1 to visit 2 in the worst 10th percentile (loss of 8 points) or having the change in Trails B score from visit 1 to visit 2 in the worst 10th percentile (50 seconds longer). Participants with cognitive impairment at baseline by a given test were excluded from the longitudinal analysis by the given test.

Other Measures

Demographic characteristics included age, education, and race. Lifestyle factors included alcohol consumption and smoking history. Participants were asked about a physician diagnosis of hypertension, diabetes, stroke, and coronary heart disease (angina, myocardial infarction, or congestive heart failure). The four conditions were summed up to create a cardiovascular comorbidity score with possible range 0–4. Quality of life measures included self-rated health and the Short Form Health Survey (SF-12) Mental Health Composite Scale score (MCS) that was used as a measure of depressive symptoms (Ware et al. 1998). Physical measures performed included height (stadiometer), and weight (balance beam or digital scale). Height and weight were used to calculate body mass index as weight in kilograms divided by the square of height in meters. Serum creatinine (SCr) was measured on previously thawed specimens collected in the morning from MrOS participants at

baseline examination and centrally stored at -120°C using the Roche COBAS Integra 800 automated analyzer (Roche Diagnostics Corp., Indianapolis, IN) using a variation of the Jaffe enzymatic method. Kidney function was expressed as estimated glomerular filtration rate (eGFR) using standardized SCr based formula derived using the Chronic Kidney Disease – Epidemiology (CKD-EPI) equation (Levey et al. 2009).

Statistical Analysis

We used quartiles of the serum phosphate as the primary predictor (Q1, 1.8–2.8 mg/dL; Q2, 2.9–3.1 mg/dL; Q3, 3.2–3.4 mg/dL; Q4, 3.5–6.8 mg/dL). Differences in baseline characteristics according to the quartile (Q) of phosphate level were compared using chi-square tests for categorical variables, analysis of variance for continuous variables with normal distributions, and non-parametric Kruskal-Wallis tests for variables with skewed distributions. Logistic regression models were used to examine the association between baseline phosphate level and odds of cognitive impairment and odds of decline between baseline and follow-up exam. In these logistic models Q1 was used as the reference group. Tests for a linear trend across quartiles were performed by including the predictor (ordinal variable, four levels) as an independent variable. Base models were adjusted for age and site. Final multivariable models included covariates that were significantly associated with phosphate levels at baseline with a p-value <0.1 or known risk factors for cognitive impairment in the MrOS cohort; age, site, race/ethnicity, education, SF-12 MCS score, self-reported health status, smoking status, alcohol use, eGFR, cardiovascular comorbidity score were included in the multivariable models. The Hosmer-Lemeshow test, Deviance, Pearson Goodness-of-Fit statistics and logistic regression diagnostics were conducted to verify the goodness-of-fit of the proposed models.

In secondary analysis we considered stroke as a possible mediator for the relationship between serum phosphate and cognitive function, and therefore ran models excluding and including those participants with a history of stroke to assess the change in point estimates. We also performed sensitivity analyses by imputing cognitive impairment via Trails B for men without baseline Trails B testing using three approaches: assuming those with missing Trails B to be 1) cognitively impaired, 2) not cognitively impaired, and 3) those with 3MS score <88 to be cognitively impaired while those with 3MS score ≥ 88 to be not cognitively impaired. Since the results of these sensitivity analyses were similar to those of the primary analysis, only the findings of the primary analysis are presented in this paper.

All significance levels reported were two-sided and all analyses were conducted using SAS version 9.3 (SAS Institute Inc, Cary, NC).

RESULTS

Characteristics of the 5,529 men in the cohort according to quartile of serum phosphate are presented in Table 1. Men in the higher quartiles of serum phosphate were less likely to report their health as good or excellent, were more likely to report past or current smoking, and had a higher burden of cardiovascular conditions, higher serum creatinine, and lower eGFR than men in lower phosphate quartiles.

Serum Phosphate and Baseline Cognitive Function

Among the cohort of 5,528 men with baseline serum phosphate and 3MS data, the number of men who were classified as cognitively impaired at baseline based on having a 3MS score <88 were 160 (12.9%), 175 (11.8%), 173 (12.6%), and 201 (14.0%) in Q1, Q2, Q3, and Q4 of phosphate, respectively. The odds of cognitive impairment in the higher serum phosphate quartiles were not significantly different than the odds of impairment in Q1 in both minimally adjusted and fully adjusted models (Table 2).

The total number of men who had baseline serum phosphate and Trails B testing was 5,403. The number of men who were classified as cognitively impaired at baseline defined as a Trails B completion time >1.5 SD above sample mean were 93 (7.7%), 121 (8.4%), 132 (9.8%), and 152 (10.9%) in Q1, Q2, Q3, and Q4 of phosphate, respectively. Compared with men in the first phosphate quartile, the odds ratios for cognitive impairment by Trails B performance in the final multivariable models were 1.12 (95% CI 0.83–1.52), 1.31 (95% CI 0.97–1.77), and 1.45 (95% CI 1.08–1.94) in men in the Q2, Q3, and Q4 of phosphate respectively (p-trend 0.007) (Table 2).

Serum Phosphate and Cognitive Decline

Compared with men who were not included in the longitudinal analyses examining cognitive decline (n=583 for change in 3MS score and n=677 for change in Trails B test), those without cognitive impairment at baseline who had repeated cognitive testing (n=3,717 for 3MS and n=3,713 for Trails B test) and were included in the longitudinal analyses had better 3MS scores and Trails B test times at baseline (Figure 1, Supplemental Table 1). In addition, they were younger, more likely to be Caucasian, more educated, had lower prevalence of comorbidities and cardiovascular disease burden, had higher eGFR, and lower SF-12 MCS score. There were no statistically significant differences in baseline serum phosphate between those included in the analysis and those eligible

At follow-up, 385 of 3,717 men met criteria for cognitive decline in global cognitive function as determined by a decrease of 3MS score of at least 8 points (worst decile of change), and 377 of 3,713 men met criteria for cognitive decline in executive function as determined by an increase in Trails B time of at least 50 seconds (i.e. worst decile of change). Higher levels of serum phosphate were not related to the odds of decline between baseline and follow-up exams as defined by the 3MS examination. Higher phosphate level was not associated with risk of decline in executive function as assessed by longitudinal change in Trails B score with fully adjusted OR 0.94 (0.69–1.28), 0.96 (0.70–1.32), 1.21 (0.89–1.66) for men in the 2nd, 3rd, and 4th versus the bottom quartile (referent group) of serum phosphate (p-trend 0.22) (Table 3).

DISCUSSION

In this study of community-dwelling older men, we found that higher serum phosphate level was independently associated with greater odds of impairment in executive function. However, among men with preserved executive function at baseline, higher phosphate level was not associated with risk of subsequent decline in executive function. We found no

association between serum phosphate level and impaired global cognitive function at baseline or the risk of subsequent decline in global cognitive function.

To our knowledge, our study is the first investigation to determine the association between phosphate level and cognitive function in a population of older community-dwelling men. There is scarce data about the relationship between serum phosphate and cognitive function in individuals not selected on the basis of kidney disease. One study reported an independent association between higher serum phosphate and lower Kidney Disease Quality of Life Cognitive Function Score in a mixed cohort of participants with CKD and ESRD (Kurella et al. 2004b). In a study by Shavit et al, a univariate analysis reported a significant correlation between cognitive decline and high plasma phosphate levels (>6 mg/dL, $p=0.034$) though the association was not significant in the multivariate analysis (Shavit et al. 2014). An animal study using a murine model of CKD showed that high phosphate levels decrease endothelium dependent relaxation and endothelium integrity (Six et al. 2012). In vitro, phosphate exhibited a direct vasoconstrictor effect on aortic rings. A high-phosphorus diet (1.3%) increased phenylephrine-induced contraction and lowered acetylcholine-induced relaxation of aortic rings ex vivo, both in non-CKD and CKD mice (Six et al. 2012). Elevated phosphate also induces vascular smooth muscle cell calcification and increases cellular expression of the bone-specific transcription factor (Jono et al. 2000). It is possible that white matter changes mediate the relationship between higher phosphate and worse executive function (Santiago et al. 2015); unfortunately, our study does not include imaging that would allow for testing of this hypothesis. While cerebrovascular disease might be a mediator of an association between higher phosphate and cognitive impairment, five studies in different cohorts (Aronson et al. 2013; Foley et al. 2008; Slinin et al. 2011; Tonelli et al. 2005; Wannamethee et al. 2013) as well as a large meta-analysis did not find an association between higher phosphate level and stroke: the relative risk of phosphate (1 mg/dL) for stroke was 1.00 (95% CI 0.97–1.05) (Li et al. 2014). In our study, the association between the highest quartile of phosphate and cognitive impairment as defined by poor executive function persisted despite adjustment for burden of cardiovascular conditions including a history of stroke and did not change in sensitivity analysis when participants with a stroke history were excluded. However, we did not find evidence that higher phosphate levels were related to the risk of decline in executive function. The absence of an association between higher phosphate and risk of decline in executive function may be in part due to exclusion of men with baseline impairment from longitudinal analyses and higher competing risk of mortality among men with higher baseline phosphate (Dominguez et al. 2013).

Many hormones are involved in phosphorus homeostasis and some of them might play a role in cognition. These substances include parathyroid hormone (PTH), vitamin D, fibroblast growth factor 23 (FGF-23) and its cofactor glucuronidase klotho (Lederer 2014). Some of the hormones are active in the brain and their levels are associated with cognitive performance. For example, in a study of 263 prevalent hemodialysis patients higher FGF-23 was independently associated with a lower memory score per doubling of FGF-23 level. There was evidence of a trend across quartiles of FGF 23 level with executive function. In addition, impairment of spatial learning and memory was reported in transgenic mice overexpressing human FGF-23 (Liu et al. 2011). Higher plasma klotho levels were associated with smaller 3-year decline in cognitive function as defined by performance on

3MS in a cohort of community dwelling older adults without dementia in Italy (Shardell et al. 2015). There is mixed evidence relating hyperparathyroidism (Lourida et al. 2015) and lower levels of vitamin D (Brouwer-Brolsma and de Groot 2015) to cognitive impairment and dementia. However, in a cohort of veterans with advanced CKD, neither vitamin D, PTH, nor FGF-23 levels were independently associated with cognitive performance (Jovanovich et al. 2014). Further research is needed to evaluate the role of the bone metabolism parameters in cognitive performance in individuals with and without kidney disease.

This study has a number of strengths including the comprehensively characterized cohort of older men and repeated assessments of global cognition and executive function. The men were not selected on the basis of level of cognitive function or kidney disease. The study also had several limitations. The participants were mostly healthy, Caucasian, elderly, community-dwelling men; therefore, findings might not be generalizable to other populations. The distribution of the serum phosphate values was narrow. The study might have been underpowered to detect an association because of healthy participant population and low prevalence of cognitive impairment. Although widely accepted measures of cognition in older people were used, no uniform definition of cognitive impairment or decline exists for Trails B testing. Without Trails A test, the results of the Trails B testing can be attributed to changes in psychomotor speed as well as changes in the executive cognitive function. In addition, the observational study design cannot address the issue of causality, and thus it is unclear whether phosphorus itself is implicated in the causal mechanism leading to impairment in executive function or whether it is a marker for different metabolic pathway.

We found an independent association between higher serum phosphate level and worse executive function defined by Trails B testing in community dwelling elderly men at baseline. There was no association between serum phosphate and global cognitive performance as measured by the 3MS examination. Among men without cognitive impairment at baseline, phosphate levels were not related to risk of cognitive decline. Further studies that include women and a more comprehensive battery of neuropsychiatric testing are warranted to further evaluate whether serum phosphate is an independent determinant of age-related changes in cognitive function and to evaluate potential mechanisms underlying any association.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key points

- Higher phosphate levels are associated with cardiovascular morbidity and mortality. We used a prospective cohort of 5,529 community dwelling elderly men enrolled in the Osteoporotic Fractures in Men (MrOS) study to determine the association between serum phosphate and cognitive function.
- We measured baseline serum phosphate, baseline cognitive function, and change in cognitive function between baseline and follow-up exams an average of 4.6 years later using the Modified Mini-Mental State (3MS) examination and Trails B.
- We found an independent association between higher serum phosphate level and worse executive function defined by Trails B testing in community dwelling elderly men at baseline. There was no association between serum phosphate and global cognitive performance as measured by the 3MS examination.
- Among men without cognitive impairment at baseline, phosphate levels were not related to risk of cognitive decline.

Figure 1.
Participant Flow

Table 1
Baseline Characteristics of the Study Participants by Quartile of Serum Phosphate (n=5529)

Characteristic	Quartile* of Phosphate, mg/dl				P-value
	Q1 n=1238	Q2 n=1481	Q3 n=1378	Q4 n=1432	
Age, years, mean (SD)	73.2 (5.7)	73.5 (5.8)	73.9 (5.9)	73.8 (6.1)	0.02
Caucasian race, n (%)	1104 (89.2)	1355 (91.5)	1249 (90.6)	1292 (90.2)	0.23
Education, categories, n (%)					0.06
Less than high school	95 (7.7)	114 (7.7)	78 (5.7)	91 (6.4)	
High school	241 (19.5)	250 (16.9)	234 (17.0)	271 (18.9)	
College or More	902 (72.9)	1117 (75.4)	1066 (77.4)	1070 (74.7)	
Self-reported good or excellent health status, n (%)	1092 (88.2)	1281 (86.6)	1192 (86.5)	1166 (81.5)	<0.001
Smoking status, n (%)					<0.001
Never	497 (40.1)	568 (38.4)	526 (38.2)	472 (33.0)	
Past	701 (56.6)	875 (59.1)	800 (58.1)	899 (62.8)	
Current	40 (3.2)	37 (2.5)	52 (3.8)	61 (4.3)	
Alcohol use, drinks per week, mean (SD)	3.9 (5.9)	4.1 (6.4)	4.2 (6.7)	4.9 (7.8)	0.45
Cardiovascular comorbidity score [†] (0–4), n (%)					<0.001
None	566 (45.7)	660 (44.6)	581 (42.2)	509 (35.5)	
1–2	639 (51.6)	770 (52.0)	740 (53.7)	816 (57.0)	
3	33 (2.7)	51 (3.4)	57 (4.1)	107 (7.5)	
Body mass index, kg/m ² , mean (SD)	27.3 (3.7)	27.3 (3.8)	27.4 (3.7)	27.6 (4.1)	0.22
eGFR, ml/min/1.73m ² , mean (SD)	76.2 (13.9)	75.5 (14.6)	75.1 (14.7)	73.2 (17.4)	<0.001
SF-12 MCS score, mean (SD)	55.8 (6.9)	55.4 (7.0)	55.8 (6.7)	55.3 (7.4)	0.28
Serum creatinine, mg/dl, mean (SD)	1.0(0.2)	1.0(0.3)	1.0(0.2)	1.1(0.4)	<0.001
3MS score (0–100), mean (SD)	93.3 (5.8)	93.4 (5.7)	93.3 (5.9)	93.1 (6.3)	0.75
Trails B total time (0–300 sec), mean (SD)	132.0 (56.3)	132.5 (58.1)	136.9 (59.4)	137.7 (61.4)	0.02

* Quartile ranges: Q1, 1.8–2.8 mg/dL; Q2, 2.9–3.1 mg/dL; Q3, 3.2–3.4 mg/dL; Q4, 3.5–6.8 mg/dL.

[†] History of one or more selected medical conditions including hypertension, diabetes, stroke, and coronary heart disease (defined as one of the following conditions: angina, myocardial infarction, or congestive heart failure)

Table 2

Association between Serum Phosphate and Odds of Cognitive Impairment at Baseline

Impairment at Baseline	Overall Cohort, n	Odds Ratio (95% CI) by Quartile* of Phosphate				P-trend
		Q1	Q2	Q3	Q4	
Defined by 3MS score [‡]	5528	n=1238	n=1480	n=1378	n=1432	
Number impaired	709	160	175	173	201	
Model 1**	5528	1.00 (referent)	0.89 (0.71–1.13)	0.91 (0.72–1.16)	1.05 (0.83–1.32)	0.60
Model 2 [‡]	5517 [§]	1.00 (referent)	0.95 (0.74–1.22)	1.05 (0.82–1.35)	1.12 (0.87–1.44)	0.26
Defined by Trails B score [¶]	5403	n=1215	n=1446	n=1352	n=1390	
Number impaired	498	93	121	132	152	
Model 1**	5403	1.00 (referent)	1.06 (0.80–1.42)	1.18 (0.88–1.56)	1.35 (1.02–1.78)	0.02
Model 2 [‡]	5393	1.00 (referent)	1.12 (0.83–1.52)	1.31 (0.97–1.77)	1.45 (1.08–1.94)	0.007

* Quartile ranges: Q1, 1.8–2.8 mg/dL; Q2, 2.9–3.1 mg/dL; Q3, 3.2–3.4 mg/dL; Q4, 3.5–6.8 mg/dL

[‡] Cognitive impairment at baseline defined as a 3MS score of <88 at the baseline visit

** adjusted for age and site

[‡] adjusted for age, site, race, education, self-reported health status, smoking status, alcohol use, eGFR, cardiovascular comorbidity score (hypertension, diabetes, stroke, and coronary heart disease), and SF-12 MCS score[§] in this model, only 707 were impaired[¶] Cognitive impairment at baseline defined as a Trails B completion time > 1.5 SD above sample mean at baseline visit (>223.2).

Table 3
Association between Serum Phosphate and Odds of Incident Cognitive Decline during Follow-up

Incident Impairment at Follow-up	Overall Cohort, n	Odds Ratio (95% CI) by Quartile* of Phosphate				P-trend
		Q1	Q2	Q3	Q4	
Defined by 3MS score [†]	3717	n=874	n=1012	n=922	n=909	
Number impaired	385	98	94	106	87	
Model 1**	3717	1.00 (referent)	0.80 (0.58–1.09)	1.00 (0.74–1.36)	0.84 (0.61–1.16)	0.61
Model 2 [‡]	3712 [§]	1.00 (referent)	0.80 (0.59–1.09)	1.05 (0.78–1.43)	0.89 (0.64–1.22)	0.89
Defined by Trails B score [¶]	3713	n=885	n=1012	n=915	n=901	
Number impaired	377	89	96	89	103	
Model 1**	3713	1.00 (referent)	0.92 (0.68–1.26)	0.92 (0.67–1.27)	1.16 (0.85–1.58)	0.34
Model 2 [‡]	3707	1.00 (referent)	0.94 (0.69–1.28)	0.96 (0.70–1.32)	1.21 (0.89–1.66)	0.22

* Quartile ranges: Q1, 1.8–2.8 mg/dL; Q2, 2.9–3.1 mg/dL; Q3, 3.2–3.4 mg/dL; Q4, 3.5–6.8 mg/dL

[†] Incident impairment defined as having the change in 3MS score from visit 1 to visit 2 in the lowest 10th percentile (loss of 8 points)

** adjusted for age and site

[‡] adjusted for age, site, race, education, self-reported health status, smoking status, alcohol use, eGFR, cardiovascular comorbidity score (hypertension, diabetes, stroke, and coronary heart disease), and SF-12 MCS score

[§] in this model, 383 were impaired as defined by 3MS score

[¶] Incident impairment defined as having the change in Trails B score from visit 1 to visit 2 in the lowest 10th percentile (50 seconds longer)